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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/846,588	05/01/2001	Steven A. Goldman	19603/3232 (CRF D-2587B)	4784
7590	06/29/2005		EXAMINER NGUYEN, QUANG	
Michael L. Goldman, Esq. NIXON PEABODY LLP Clinton Square P.O. Box 31051 Rochester, NY 14603-1051			ART UNIT 1633	PAPER NUMBER
DATE MAILED: 06/29/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/846,588

Applicant(s)

GOLDMAN ET AL.

Examiner

Quang Nguyen, Ph.D.

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-6, 13-18, 28-37, 44-46 and 55-58 is/are pending in the application.
- 4a) Of the above claim(s) 31, 32 and 55-58 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 13-18, 28-30, 33-37 and 44-46 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_

### DETAILED ACTION

Applicant's amendment filed on 4/11/05 has been entered.

Amended claims 1-6, 13-18, 28-37, 44-46 and new claims 55-58 are pending in the present application.

Newly submitted claims 55-58 contain embodiments directed to inventions that are independent or distinct from the invention originally claimed for the following reasons:

New claims 55-58 contain embodiments drawn to a method of inducing addition of neurons in post-natal and adult brain of a subject or a method of treating a neurodegenerative condition of the neostriatum requiring **a specific combination** of a nucleic acid construct encoding a brain-derived neurotrophic factor and a nucleic acid construct encoding noggin (claims 55-57) or requiring **a specific combination** of a brain derived neurotrophic factor and a nucleic acid construct encoding a noggin (claim 58). These are distinct methods from the elected method of inducing neuronal production in post-natal and adult brain of a subject or a method of treating a neurodegenerative condition by injecting a nucleic acid construct encoding a brain-derived neurotrophic factor, neurotrophin-4/5 or neurotrophin-3 or introducing the same neurotrophic factors into any one or all of a subject's caudate nucleus, and putamen to treat a neurodegenerative condition from the invention originally elected (Invention of Group I, see Office Action mailed on 2/28/02 and Amendment dated 4/9/02). This is because the methods contain different starting materials (the encoded neurotrophic factors such as brain-derived neurotrophic factor, neurotrophin-4/5, neurotrophin-3 are

Art Unit: 1636

distinct molecules structurally and biochemically from noggin which is an inhibitor of bone morphogenic proteins; and the specific combination of brain-derived neurotrophic factor with noggin) and therefore they would require different technical consideration for attaining the desired results. Moreover, it would be undue burden for the examiner to search both structurally distinct molecules that have no common core structure and/or biochemical activities, for this instance a brain-derived neurotrophic factor and a noggin.

Additionally, it is noted that Applicants also elected, with traverse, Huntington's disease as a neurodegenerative condition (Please note that this is not a species election for the reasons already set forth in the Office Action mailed on 2/28/02).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 55-58 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application also contains claims 31-32 drawn to an invention nonelected with traverse in the Amendment filed on 4/9/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Accordingly, amended claims 1-6, 13-18, 28-30, 33-37 and 44-46 are examined on the merits herein.

***Response to arguments***

With regard to new claims 55-58, Applicants argue that the combination of brain-derived neurotrophic factor and noggin was never raised in the previously-imposed restriction requirement nor in the applicant's responsive election, and therefore it can not be said that applicants made an election that excluded the subject matter of the new claims. On the contrary, the combination of brain-derived neurotrophic factor and noggin in new claims is entirely consistent with what Applicants previously elected and that they should now receive a full examination.

Please note that the combination of brain-derived neurotrophic factor and noggin was never raised in the previously imposed restriction requirement because original claims do not recite any combination of a diverse groups of neurotrophic factors that share no common core structure and/or biochemical activities (e.g., BDNF and neurotrophins of Group I; Insulin-like growth factor-1 of Group II; noggin or an inhibitor of bone morphogenic proteins of Group III), let alone for the specific recombination of BDNF and noggin now claimed. Moreover, the elected Group I is directed to methods of inducing neuronal production in post-natal and adult brain and spinal cord or of recruiting neurons to a subject's brain or of treating a neurodegenerative condition comprising injecting a nucleic acid construct encoding a brain-derived neurotrophic factor, neurotrophin-4/5 or neurotrophin-3 or introducing the same neurotrophic factors into the subject.

See the preceding paragraphs for the reasons why claims 55-58 are withdrawn from consideration as being not directed to the original presented invention.

***Response to Amendment***

The Declaration filed on 12/06/04 under 37 CFR 1.132, **which should be properly filed under 37 CFR 1.131**, has been considered by the examiner and it is sufficient to overcome the Benrais et al. reference.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 28-30, 33-37 and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the previous Office action mailed on 6/2/04 (pages 4-12).

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification the construction of a replication defective recombinant adenovirus pAd5-CMV:BDNF:IRES:hGFP expressing brain-derived neurotrophic factor (BDGF) under CMV control and humanized green fluorescent protein (hGFP) under internal ribosomal entry site control. The recombinant adenovirus was injected into the lateral ventricles of adult rats that were treated for 18 days thereafter with the mitotic marker bromodeoxyuridine (BrdU). Three weeks after injection, ELISA analysis revealed that the cerebral synovial fluid BDNF level of AdBDNF-injected animals was about 1 ug/g, whereas BDNF was undetectable in cerebral synovial fluid (CSF) of control animals. *In situ* hybridization revealed that BDNF and GFP mRNAs were largely restricted to the ventricular wall (ependymal surface). In AdBDNF-injected rats, the olfactory bulb exhibited a 2.44-fold increase in the number of BrdU+ $\beta$ III tubulin+ neurons relative to AdNull (AdCMV:hGFP) controls. Additionally, ventricular AdBDNF infection also induced neuronal recruitment to the neostriatum as evidenced by the presence of BrdU+ $\beta$ III tubulin+ neurons, many of which also expressed glutamic acid decarboxylase, cabindin-D28 and DARPP-32, markers of medium spiny neurons of the neostriatum. These newly generated neurons survived at least 5-8 weeks after viral induction.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant claimed invention which is drawn to a method of treating Huntington's disease by injecting a nucleic acid construct encoding a brain-derived neurotrophic factor into a subject's lateral ventricles or ventricular zone wall or

introducing a brain-neurotrophic factor into a subject under conditions effective to treat said disease for the reasons to be discussed below.

**(a) *The breadth of the claims.*** With respect to the elected invention, claims 28-30 and 33-37 are drawn to a method of treating encompassing delaying, slowing, abrogating and reverse the progression of the Huntington's disease in any subject by injecting a nucleic acid construct encoding for a brain-derived neurotrophic factor into a subject's lateral ventricles or ventricular zone wall, whereas claims 44-46 are drawn to a method of treating Huntington's disease comprising introducing a brain-derived neurotrophic factor into any one or all of any subject's caudate nucleus, and putamen under conditions effective for the treatment.

**(b) *The state of the prior art and the unpredictable of the prior art.*** At the effective filing date of the present application (05/01/2000), the art for treating any neurodegenerative disease using *in vivo* gene therapy or any neurotrophic factor was and continues to be immature and unpredictable with respect to the attainment of therapeutic effects, let alone for treating specifically Huntington's disease with a brain-derived neurotrophic factor (elected invention). This is evidenced by the reviews of During et al. (Mol. Med. Today 4:485-493, 1998), Shihabuddin et al. (Mol. Med. Today 5:474-480, 1999), Pencea et al. (J. Neuroscience 21:6706-6717, 2001) and Emerich (Exp. Opin. Biol. Ther. 1:467-479, 2001). During et al. stated "Which neurological disease are the best targets for gene therapy, given that currently targeted neurological diseases are determined largely by the availability of animal models and might not be the most responsive to a gene therapy approach?" and "How well do current animal



Art Unit: 1636

models of central nervous system (CNS) disease predict clinical efficacy of novel therapeutic strategies?" (page 490, in "The outstanding questions"). Emerich stated "Despite the optimism surrounding the potential of neuroprotection, several fundamental issues are unresolved, each with direct relevance to the development of therapies. For instance, we really don't know the cause of the cell death that occurs in the striatum of HD patients. Without this understanding, we will never reach the holy grail of HD research: preventing the disease by preventing the genetic abnormality" (page 475, col. 1, second paragraph); "While some clinical trials are ongoing (using cellular delivery of neurotrophic factors and systemic administration of riluzole and coenzyme Q10) no clear cut successes are evident" (page 475, col. 2, bottom of the middle paragraph); and "Future gene therapy approaches will certainly be attempted but the invasive nature and the lack of adequate control over gene regulation and dosing make these therapies currently untenable for widespread use" (page 475, col. 2, bottom of the last paragraph). Pencea et al. also stated in 2001 that "[I]f BDNF could be provided exogenously, it could potentially serve to promote the formation of numerous new neurons in extensive regions of the mammalian brain. Our future studies will seek to reveal whether BDNF can rescue degenerated neurons or help achieve replacement of neurons already lost as a result of a disease process." (page 6716, col. 2, bottom of first full paragraph). On the basis of the same set of data disclosed in the present specification, Applicants stated in a post-filing peer-reviewed journal "[o]ur hope is that if these cells prove functional and able to survive, then AdBDNF-induced striatal neurons might be able to delay, abrogate, or reverse striatal neurodegenerative disease. Nonetheless, it remains

Art Unit: 1636

to be seen whether these AdBDNF-induced neurons can functionally integrate, both with resident striatal neurons and nigrostriatal afferents, whether they can survive longer than the 5-8 weeks that we have noted, and whether they can survive the primary disease process better than the cells they are intended to replace" (page 6731, col. 1, first paragraph, Benraiss et al. J. Neuroscience 21:6718-6731, 2001; IDS).

With respect to claims drawn to *in vivo* gene therapy, it is well known in the art that the lack of optimal vectors, the lack of stable *in vivo* transgene expression as well as the adverse host immune responses against delivered vectors are some of factors limiting the effectiveness of gene therapy for attaining any therapeutic effect. With respect to claims drawn to a method of treating a Huntington's disease by introducing a brain-derived neurotrophic factor into any one or all of a subject's caudate nucleus and putamen, it is well known in the art that central nervous system (CNS) neurons lack intrinsic ability to mount a regenerative response, particularly in a post-natal or an adult subject (Jackowski; British Journal of Neurology 9:3030-317, 1995). Furthermore, it is not known in the art the specific recited brain regions contain any stem cell or progenitor cell population that is capable of responding to a delivered brain-derived neurotrophic factor in a manner that yields the therapeutic effects for treating Huntington's disease as contemplated by Applicants (see Shihabuddin et al., section titled "Location and identity of progenitors").

**(c) The amount of direction or guidance provided.** As the term "treatment" encompasses delaying, slowing, abrogating and reverse the progression of the Huntington's disease, the instant specification fails to offer any guidance for a skilled

Art Unit: 1636

artisan on how to achieve any of the aforementioned therapeutic effects. There is no correlation between the reported presence of BrdU+ $\beta$ III tubulin+ neurons in the neostriatum with any of the therapeutic effects contemplated by Applicants. Since the prior art at the effective filing date of the present application (5/1/02) does not provide such guidance, it is incumbent upon the instant specification to do so. With the lack of guidance provided by the present disclosure and in light of the totality of the state of the art as discussed above, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed. This is because there is no evidence of record indicating or suggesting that an efficient number of striated neurons in the appropriate locations of the brain has been generated to yield any therapeutic effects. Additionally, it is unclear whether these newly induced striated neurons can form functional junctions with preexisting neurons or that these newly generated striated neurons can survive better than the neurons they intend to replace for any significant period of time under the disease conditions to yield any desired therapeutic effects. The present disclosure also fails to provide any *in vivo* example (part of guidance) showing any therapeutic effects has been attained or achieved.

Although Kirschenbaum et al. (Proc. Natl. Acad. Sci. USA 92:210-214, 1995) teach that BDNF is the only neurotrophin tested (BDNF, neurotrophin-3, NGF) that can affect the differentiation and survival of newly generated neurons in the adult rat brain *in vitro* (see abstract and Table 1), the enhanced neuronal survival property of BDNF is still controversial. This is because Ahmed et al. (J. Neurosci. 15:5765-5778, 1995) have demonstrated that BDNF enhances the differentiation but not the survival of CNS stem

Art Unit: 1636

cell-derived neuronal precursors (see abstract). Furthermore, it has been reported by various independent groups that BDGF has no protective effect on striatal neurons in a rodent model of Huntington's disease as evidenced by the teachings of Araujo et al. (Neuroscience 81:1099-1110, 1997), Anderson et al. (Proc. Natl. Acad. Sci. 93:7346-7351, 1996) and Frim et al. (Neuroreport 4:367-370, 1993; Abstract only). It should also be noted that the physiological art is recognized as unpredictable (MPEP 2164.03). As such, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

With respect to amended claims 44-46, in addition to the issues discussed above, there is no teaching regarding on how an effective amount of any brain-derived neurotrophic factor can be maintained in the specific recited brain regions for a sufficient period of time to elicit the desired therapeutic effects or whether the recited brain regions do contain any stem cell or progenitor cell population that is capable of responding to the delivered neurotrophic factor in a manner (e.g., induced proliferation and differentiation into proper neuron populations) that yields the therapeutic effects for treating Huntington's disease as contemplated by Applicants. As such, with the lack of sufficient guidance provided by the instant specification and in light of the totality of the state of the art discussed above, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

**(d) The amount of experimentation provided.** There is no relevant example indicating or suggesting any therapeutic effects has been obtained for treating

Art Unit: 1636

a Huntington's disease in any subject by providing a brain-derived neurotrophic factor or a nucleic acid construct encoding a brain-derived neurotrophic factor.

Accordingly, due to the lack of direction or guidance provided by the specification regarding to the issues set forth above, the unpredictability of the gene therapy art and physiological art, particularly for attaining therapeutic effects in treating Huntington's disease, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

### ***Response to Arguments***

Applicants rely mainly on Dr. Steven A. Goldman's Third Declaration under 37 C.F.R. 1.132 filed on 12/27/04 and Dr. Flint Beal's Declaration under 37 C.F.R. 1.132 filed on 12/27/04 to respond the above rejection.

The Declarations under 37 CFR 1.132 filed on 12/27/04 and 12/27/04 are insufficient to overcome the rejection of amended claims 28-30, 33-37 and 44-46 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph, as set forth above for the following reasons:

Firstly, the significant deceleration in motor degeneration and enhanced survival observed in the R6/2 mice treated **with both AdBDNF and AdNoggin**, relative to both their saline and AdNull-treated R6/2 control mice are not relevant to the presently elected invention which does not involved the specific co-administration of both brain derived neurotrophic factor and noggin or the nucleic acid construct(s) encoding both of these neurotrophic factors.

Secondly, it is also apparently clear from the second and third Declaration of Dr. Goldman that brain derived neurotrophic factor (BDNF) treatment **alone** is not sufficient to induce a sufficient effective number of new neurons (<1% of the striated neuronal population) to yield any therapeutic effects contemplated by Applicants such as a significant deceleration in motor degeneration and/or enhanced survival in **R6/2 mice treated with AdBDNF alone**.

Thirdly, there is no factual evidence provided indicating that any therapeutic effects such as delaying, slowing, abrogating and reverse the progression of the Huntington's disease in any subject (all of which are encompassed by the scope of treatment), including in the R6/2 mouse model has been attained or achieved by the brain derived neurotrophic treatment alone (elected invention).

Fourthly, the Declaration of Dr. Beal clearly states "In broad terms, these findings indicate that induced neurogenesis may be viewed as **a potential therapeutic modality for HD**. Specifically, BDNF overexpression is necessary and sufficient to permits the generation in the adult brain of new striatal neurons of the identical phenotype lost in HD" (page 2, bottom of paragraph 6). However, Dr. Beal does not further provide any factual evidence indicating that any therapeutic effects such as delaying, slowing, abrogating and reverse the progression of the Huntington's disease in any subject, including in the R6/2 mouse model has been attained or achieved by the brain derived neurotrophic treatment alone (elected invention).

Therefore, in light of the totality of the state of the art for treating Huntington's disease as discussed above, coupled with the lack of sufficient guidance provided by

Art Unit: 1636

the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

Accordingly, amended claims 28-30, 33-37 and 44-46 are rejected under 35 U.S.C. 112, first paragraph for the reasons set forth above.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Amended claims 1-5 and 13-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss et al. (U.S. Patent No. 6,071,889 with an effective filing date of 6/7/1995) for the same reasons already set forth in the previous Office Action mailed on 6/2/05 (pages 12-14).

With respect to the elected invention, Weiss et al. teach a method comprising the step of administering (including injection) a nucleic acid sequence comprising a sequence encoding BDNF into a CNS ventricle, specifically the lateral ventricle of the forebrain, of a mammal (juvenile and adult) for inducing the proliferation and differentiation of neural stem cells *in vivo* (see Summary of Invention, cols. 26-29; col. 27, lines 3-11; and the claims). Weiss et al. also disclose that any expression vector

Art Unit: 1636

known in the art can be used to express BDNF as long as it has a promoter that is active in the cell, and appropriate termination and polyadenylation signals. Expression vectors such as retroviral vectors, adenovirus vectors, adeno-associated virus vectors, HSV vectors, vaccinia virus vectors and others (col. 29, lines 44-57; col. 20, lines 61-63); mammalian cell specific promoters such as those of tyrosine hydroxylase, DBH, GFAP, NSE, NF, phenylethanolamine N-methyltransferase as well as retroviral LTR, SV40 and CMV promoters can be utilized (col. 29, lines 17-25). Weiss et al. specifically teach that the infected subependymal cells migrate out into the striatum where they differentiate into neuronal cells (see col. 28, lines 48-51; col. 50, lines 49-55), and that the striatum consists of the caudate and putamen (see col. 3, lines 39-40).

Since the method taught by Weiss et al. has the same starting materials and the same method steps as the presently claimed methods, it is inherent that the method of Weiss et al. also induces addition of neurons in post-natal and adult brain in a subject (e.g., to any one or all of the caudate nucleus and the putamen of the subject). Furthermore, it is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. In re Woodruff, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); In re Swinehart, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and Ex Parte Novitski, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

Since the teachings of Weiss et al. meet every limitation of the instant claims, the reference anticipates the instant claims.



**Response to Arguments**

Applicants' arguments related to the above rejection in the Amendment filed 12/06/04 (page 11), have been fully considered; but they are found unpersuasive.

Applicants reiterate the same arguments previously presented. Basically, Weiss fails to teach injecting a nucleic acid construct encoding a neurotrophic factor into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce neuronal production or recruit neurons to in any one or all of the caudate nucleus, and the putamen of the subject. Applicants further argue that Weiss fails to posit, specify or prove how growth factor addition to the adult brain might cause the specific addition of medium spiny pallidal projection neurons to the adult caudate nucleus and putamen. Therefore, Weiss does not provide an enabling disclosure of the present invention and thus it is not anticipatory.

Please note Weiss et al. teach clearly an enabled method comprising a step of administering (including injection) a nucleic acid sequence comprising a sequence encoding BDNF into a CNS ventricle, specifically the lateral ventricle of the forebrain, of a mammal (juvenile and adult) to induce the proliferation and differentiation of neural stem cells *in vivo* (see Summary of Invention, cols. 26-29; col. 27, lines 3-11; and the claims). Furthermore, Weiss et al. specifically teach that the infected subependymal cells migrate out into the striatum where they differentiate into neuronal cells (see col. 28, lines 48-51; col. 50, lines 49-55), and that the striatum consists of the caudate and putamen (see col. 3, lines 39-40). Since the method taught by Weiss et al. has the same starting materials and the same method steps as the presently claimed methods,

Art Unit: 1636

it is inherent that the method of Weiss et al. also induces addition of neurons in post-natal and adult brain in a subject (e.g., to any one or all of the caudate nucleus and the putamen of the subject). Furthermore, it is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. In re Woodruff, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); In re Swinehart, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and Ex Parte Novitski, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

Accordingly, amended claims 1-5 and 13-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss et al. (U.S. Patent No. 6,071,889) for the reasons set forth above.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

Art Unit: 1636

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1, 6, 13 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Weiss et al. (U.S. Patent No. 6,071,889 with an effective filing date of 6/7/1995) in view of Reeves (U.S. Patent No. 5,965,440) for the same reasons already set forth in the previous Office Action mailed on 6/2/05 (pages 18-20).

With respect to the elected invention, Weiss et al. teach a method comprising a step for administering (including injection) a nucleic acid sequence comprising a sequence encoding BDNF into a CNS ventricle, specifically the lateral ventricle of the forebrain, of a mammal (juvenile and adult) for inducing the proliferation and differentiation of neural stem cells *in vivo* (see Summary of Invention, cols. 26-29; col. 27, lines 3-11; and the claims). Weiss et al. also disclose that any expression vector known in the art can be used to express BDNF as long as it has a promoter that is active in the cell, and appropriate termination and polyadenylation signals. Expression vectors such as retroviral vectors, adenovirus vectors, adeno-associated virus vectors, HSV vectors, vaccinia virus vectors and others (col. 29, lines 44-57; col. 20, lines 61-63); mammalian cell specific promoters such as those of tyrosine hydroxylase, DBH, GFAP, NSE, NF, phenylethanolamine N-methyltransferase as well as retroviral LTR, SV40 and CMV promoters can be utilized (col. 29, lines 17-25). Weiss et al. specifically teach that the infected subependymal cells migrate out into the striatum where they differentiate into neuronal cells (see col. 28, lines 48-51; col. 50, lines 49-55), and that the striatum consists of the caudate and putamen (see col. 3, lines 39-40).

However, Weiss et al. do not specifically teach the use of any inducible or conditional promoter for expressing BDNF.

However, at the effective filing date of the present application Reeves already teaches the use of an inducible promoter, specifically a tetracycline regulated promoter, in a retroviral vector system for expressing a gene (e.g., glial derived neurotrophic factor, tyrosine hydroxylase) in a mammalian cell, including *in vivo* (see abstract and Summary of the Invention). Reeves further teaches that the disclosed retroviral tetracycline regulated system enhances the temporal and quantitative control of gene product delivery, as well as a more precise induction of gene expression relative to other tetracycline-regulated systems known in the art (col. 6, lines 2-16).

Accordingly, at the effective filing date of the present application it would have been obvious and within the level of skills for an ordinary skilled artisan to modify the method taught by Weiss et al. by utilizing an inducible promoter in a retroviral vector for expressing BDNF based on the system taught by Reeves due to the disclosed advantages offered by the tetracycline regulated system.

An ordinary skilled artisan would have been motivated to make this modification because as taught by Reeves the disclosed retroviral tetracycline regulated system enhances the temporal and quantitative control of gene product delivery (and therefore the biological effects of the delivered gene product, for this instance BDNF), as well as a more precise induction of gene expression relative to other tetracycline-regulated systems known in the art (col. 6, lines 2-16).

Art Unit: 1636

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Weiss et al., Reeves and a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### ***Response to Arguments***

Applicants' argument related to the above rejection in the Amendment filed 12/6/04 (page 12) has been fully considered.

Applicants argue mainly that Reeves does not overcome the deficiencies of Weiss for the reasons set forth by Applicants in the response to the rejection of claims 1-5 and 13-17 above.

Once again, Applicants' argument is not found persuasive for the same reasons already set forth in the response to Applicants' arguments for the rejection of claims 1-5 and 13-17 above.

### ***Conclusions***

***No claims are allowed.***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

Art Unit: 1636

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.**

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Quang Nguyen, Ph.D.

  
DAVID GUZO  
PRIMARY EXAMINER